

**REMARKS**

The Official Action dated October 5, 2004 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks and the copy of the Declaration Under 37 C.F.R. 1.132 of Dr. Sigbritt A.M. Werner, originally submitted in parent application Serial No. 09/050,366, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the title is amended to more specifically describe the claimed methods. The related application section of the specification is amended to update the status of the referenced applications. Claims 11 and 12 are amended to recite an analog as set forth in the specification, for example, at page 3, lines 17-20. Claim 12 has also been amended to correct its dependency from cancelled claim 1 to claim 11. Finally, claim 19 is added and recites the embodiment wherein recombinant human growth hormone is administered, in accordance with specific teachings in the present specification. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 11-18 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification, while enabling for methods administering recombinant human growth hormone (rhGH), does not reasonably provide enablement for treatment using all kinds of growth hormones or functional analogs thereof. The Examiner noted that while the specification discloses that analog means a substance having the same biological activity and at least 65% homology with natural occurring growth hormone, but asserted that Applicants have not shown that the various growth hormones would be effective as the exemplified rhGH formulations. The Examiner referred to the present specification as teaching unpredictability in the dosage regimen of the exemplified rhGH, let alone the

unpredictability of other kinds of growth hormones, and the Examiner referred to Holly et al, *J. Endocr.*, 118:353-364 (1988), and Salomon et al, *N. Engl. J. Med.*, 321(26):1797-1803 (1989), as detailing the variations in treatment effects with growth hormone.

However, Applicants submit that claims 11-18 are fully enabled by the present specification in accordance with the requirements of 35 U.S.C. §112, first paragraph, and, accordingly, this rejection is traversed. More particularly, Applicants submit that the recitation of "human growth hormone or an analog thereof" as set forth in claim 11 is fully enabled by the specification. Specifically, one skilled in the art recognizes that recombinant human Growth Hormone (rhGH) is produced by isolating the human Growth Hormone (hGH) gene and reproducing the hGH in high quantities by recombinant DNA techniques. Accordingly, rhGH is used interchangeably with natural human Growth Hormone for clinical use. Furthermore, one skilled in the art appreciates that an analog of human growth hormone, including an analog of recombinant human growth hormone, is defined in the specification at page 3, lines 19-20 as "a substance having the same biological activity as described here and having at least 65% homology with natural occurring growth hormone". One of ordinary skill in the art can easily determine if a substance has at least 65% homology with natural occurring human growth hormone and if it has the same biological activity as described in the specification, without undue experimentation. Particularly, the present specification provides concrete examples of measuring the effectiveness of treatment whereby one of ordinary skill in the art can easily determine if an analog is within the specified definition.

A disclosure is enabling if, from the information set forth in the specification, coupled with information known in the art, one of ordinary skill in the art can make and use the invention without undue experimentation, *United States v. Teletronics, Inc.*, 8 USPQ2d 1217, 1224 (Fed. Cir. 1988). Moreover, every aspect of a generic claim certainly need not have

been carried out by an inventor, or exemplified in the specification; rather, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention, *Genetec v. Novo Nordisc, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). Finally, a patent need not teach, and preferably omits, what is well known in the art, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). As similarly established in parent application Serial No. 09/050,366, the specification clearly defines "human growth hormone or an analog thereof", whereby one of original skill in the art will appreciate how to produce human growth hormone or an analog thereof for use in accordance with the present invention. It is therefore submitted that present claims 11-18 are fully enabled by the specification, whereby the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 11-18 were also rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner objected to the recitation of the phrase "functional analog thereof" as the present specification refers only to "analogs". This rejection is traversed. More particularly, claim 11 recites that the method comprises administering to the patient human growth hormone or an analog thereof, in accordance with the teachings of the specification. It is therefore submitted that claim 11 and claims 12-18 dependent thereon, are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby this rejection has been overcome. Reconsideration is respectfully requested.

Finally, claims 1-18 were rejected under 35 U.S.C. §103(a) as being unpatentable over Johansson et al, *Metabolism*, 44(9):1126-1129 (1995), taken with Rosen et al, *Acta Endocrinologia*, 129:195-200 (1993) and Reaven et al, *N. Eng. J. Med.*, 334(6):374-381 (1996). The Examiner asserted that Johansson et al teach that growth hormone deficient adults are insulin resistant, that serum triglyceride levels are higher in adults with growth

hormone deficiency, that hyperinsulinemia is a common feature in all other states involving insulin resistance, such as obesity, hypertension and non-insulin dependent diabetes mellitus, and that after six months of rhGH treatment, insulin insensitivity can be restored to baseline values. The Examiner asserted that Johansson et al therefore teach use of growth hormones to decrease insulin resistance associated with Metabolic Syndrome, which may include lipoprotein aberrations or hypertension. The Examiner relied on Rosen et al as showing that growth hormone deficiency alters lipoprotein metabolism and increases the risk of development of hypertension and concluded that growth hormone is important for the regulation of lipoprotein metabolism during adult life. The Examiner relied on Reaven et al as showing the changes in glucose, insulin and lipoprotein metabolism in patients with hypertension. The Examiner concluded that one skilled in the art would have immediately envisioned the use of growth hormone for treating insulin resistance in a patient having metabolic syndrome exhibiting lipoprotein aberrations or hypertension.

However, as set forth in detail below, Applicants submit that the methods defined by claims 11-18 are nonobvious over and patentably distinguishable from the combination of Johansson et al, Rosen et al and Reaven et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 11, the present invention is directed to a method for treating a patient having Metabolic Syndrome comprising Primary Insulin Resistance and exhibiting lipoprotein aberrations or hypertension. The method comprises administering to the patient human growth hormone or an analog thereof in an amount effective for decreasing lipoprotein aberrations or hypertension of the patient.

Applicants find no teaching, suggestion or reference by Johansson et al of a method for treating a patient having Metabolic Syndrome comprising Primary Insulin Resistance, particularly

to decrease lipoprotein aberrations or hypertension of a patient, as recited in claim 11. Rather, the Johansson et al reference is directed to insulin resistance of adult patients who are growth hormone deficient. The 1993 Fowelin et al study, cited by Johansson et al in the paragraph bridging pages 1128 and 1129, teaches that initial treatment of growth hormone deficient patients induced a markedly worsened insulin resistance after 6 weeks, and that after 26 weeks of growth hormone treatment, insulin sensitivity returned to base line values in the growth hormone deficient patients. Applicants find no teaching, suggestion, or reference in Johansson et al of the use of growth hormones to decrease lipoprotein aberrations or hypertension in patients who have Metabolic Syndrome comprising Primary Insulin Resistance. Therefore, one of ordinary skill in the art would not have immediately envisaged the use of growth hormones as disclosed by Johansson et al to treat a patient with Metabolic Syndrome.

Moreover, the Examiner's attention is directed to the copy of the Declaration under 37 CFR 1.132 of Dr. Sigbritt A. M. Werner, originally submitted in parent application Serial No. 09/050,366. As established in the Declaration, Dr. Werner serves as a Professor in Endocrinology and Vice President at Karolinska Institute and offers her opinions regarding the state of the art and particularly what Johansson et al teach and suggest to those skilled in the art. Opinion testimony is entitled to consideration and weight as long as the opinion is not on the ultimate legal conclusion at issue, MPEP §716, and opinion testimony regarding what the prior art taught may be entitled to considerable deference, *In re Carroll*, 202 U.S.P.Q. 571 (CCPA 1979).

According to paragraph 3 of Dr. Werner's Declaration, based on her experience in the medical fields, and particularly the field of endocrinology, it is her opinion that growth hormone deficient patients are distinct from patients who are not growth hormone deficient. Specifically, growth hormone deficient patients do not produce growth hormones and therefore their hormone

levels and their therapeutic responses to growth hormone administration differ significantly from the hormone levels and therapeutic response to growth hormone administration in a patient who is not growth hormone deficient. Thus, a therapeutic response to growth hormone administration in a growth hormone deficient patient cannot be used to predict a response to growth hormone administration in a patient who is not growth hormone deficient. Specifically, the effect of growth hormone administration on insulin resistance in a growth hormone deficient patient cannot be used to predict an effect of growth hormone administration on insulin resistance in a patient who is not growth hormone deficient.

Also, as noted at paragraph 4 of the Declaration, based on her experience in the field of endocrinology, it is Dr. Werner's opinion that an individual who has Metabolic Syndrome does not inherently exhibit growth hormone deficiency, and an individual who has growth hormone deficiency does not inherently exhibit Metabolic Syndrome.

Further, as noted at paragraph 5 of the Declaration, based on her experience in the field of endocrinology, it is her opinion that Johansson et al do not teach or suggest insulin resistance in individuals with Metabolic Syndrome and thus, cannot be used to suggest growth hormone administration to individuals having Metabolic Syndrome comprising Primary Insulin Resistance.

Thus, the Declaration establishes the understandings of one of ordinary skill in the art with respect to Johansson et al, and the differences between Johansson et al and the present invention which are evident to one of ordinary skill in the art. The Declaration is therefore entitled to consideration and weight.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). In view of the failure of Johansson et al to teach, suggest or recognize a method for decreasing lipoprotein aberrations or hypertension in a patient

with Metabolic Syndrome comprising Primary Insulin Resistance, particularly by administering human growth hormone, Johansson et al do not provide an enabling disclosure of the present invention, and therefore do not support a rejection of the claims under 35 U.S.C. §103.

Moreover, the deficiencies of Johansson et al are not resolved by Rosen et al and/or Reaven et al. That is, Rosen et al describe a study wherein subjects with growth hormone deficiency and adequate replacement therapy with glucocorticoids, thyroid hormones and gonadal steroids were studied with respect to known risk factors for cardiovascular disease. Applicants find no teaching or suggestion by Rosen et al relating to treatment of individuals with Metabolic Syndrome, particularly Metabolic Syndrome comprising Primary Insulin Resistance, or relating to such individuals exhibiting lipoprotein aberrations or hypertension.

Reaven et al describe changes in glucose, insulin and lipoprotein metabolism in patients with hypertension. Reaven et al also discuss the role of the sympathoadrenal system in the development of hypertension and the related metabolic changes, and the metabolic effects of anti-hypertensive drugs that effect the sympathoadrenal system. However, Applicants find no teaching or suggestion by Reaven et al relating to treatment of an individual having Metabolic Syndrome and comprising Primary Insulin Resistance by administering human growth hormone, particularly in an amount effective for decreasing lipoprotein aberrations or hypertension of such an individual.

In view of the failure of Rosen et al and Reaven et al to teach or suggest administering human growth hormone in order to decrease lipoprotein aberrations of hypertension in an individual having Metabolic Syndrome comprising Primary Insulin Resistance, neither of these references resolve the deficiencies of Johansson et al. Thus, these references in combination do not provide an enabling disclosure of the presently claimed methods and do not place the claimed methods in the possession of the public. Thus, the combination of

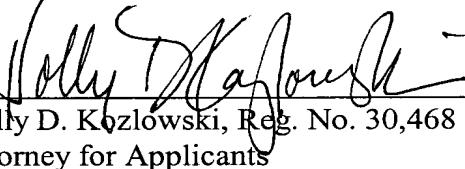
Application Serial No. 10/808,696  
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Johansson et al, Rosen et al and Reaven et al do not support a rejection of claims 11-18 under 35 U.S.C. §103. It is therefore submitted that the rejection has been overcome, and reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§103 and 112, first and second paragraphs, set forth in the Official Action, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

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